REMARKS

Claims 25-44, 55-71, and 73-103 were pending in this case.

Claims 25-44, 55-71 and 73-103 are hereby cancelled without prejudice.

Claims 104-113 are newly added.

Support for the new claims is found in the specification and claims as originally filed, including at least the following locations: ¶ 28 on page 5, ¶29 on page 6, ¶50 on page 13, ¶051 on page 14, ¶55 on page 14, ¶59 on page 15, ¶72 on page 18, ¶81 on page 21, ¶90 on page 24 and ¶96 on page 25.

No new matter is added.

Claim Rejections under 35 U.S.C. § 112, second paragraph

Claims 25-44, 75-88 and 90-101 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for reciting the phrase "has been confirmed to correlate". Claim 25-44, 75-88, and 90-101 have been canceled; therefore this rejection is moot as to those claims. Moreover, the phrase "has been confirmed to correlate" does not appear in the new claims set forth above.

For these reasons, Applicants respectfully request that the Examiner withdraw this rejection.

Claim Rejection under 35 U.S.C. § 102

Claims 75-88 and 90-100 stand rejected under 35 U.S.C. § 102(b) as being anticipated by *Fodor* (US20010053519). Claims 75-88 and 90-100 have been canceled; therefore this rejection is moot as to those claims and should be withdrawn. To the extent that this rejection applies to the new claims, this rejection is respectfully traversed.

A claim is anticipated only if each and every element of the claim as set forth is found, either expressly or inherently described, in a single prior are reference. Further, the identical invention must be shown in as much detail as contained in the claim. MPEP § 2131. Applicants respectfully assert that *Fodor* does not teach each and every element of the new claims.

The rejection of claims 75-88 and 90-100 appears to be based on a theory of inherency under which the Examiner believes *Fodor* describes gene expression assays that involve hybridizing labeled samples to an array containing every possible 10-mer sequence. Since the Examiner believes that *Fodor's* array would inherently contain oligonucleotides that bind to introns, the Examiner believes that claims 75-88 and 90-100 are anticipated.

However, even assuming *arguendo* that *Fodor's* array contained every possible 10-mer sequence, *Fodor* does not disclose a method that includes determining the expression level of a target gene using a polynucleotide complementary to an intronic sequence of a target gene, as required by the new claims. Since all claimed elements are not disclosed by *Fodor* – expressly or inherently – *that reference* does not anticipate the new claims.

For these reasons, Applicants respectfully request withdrawal of this rejection, and assert that the application is in condition for allowance.

Claim rejections under 35 U.S.C. § 103

Claims 25, 27-30, and 33-44

Claims 25, 27-30, and 33-44 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over *Fodor* in view of Duvick (USPN 7026123). Claims 25, 27-30, and 33-44 have been canceled; therefore this rejection is moot as to those claims. To the extent that this rejection applies to the new claims, Applicants respectfully traverse it.

In order to meet its burden in establishing a rejection under 35 U.S.C. §103, the Office must first demonstrate that a prior art reference, or references when combined, teach or suggest all claim elements. S*ee, e.g., KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 (2007); *Pharmastem Therapeutics v. Viacell et al.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007); MPEP § 2143(A)(1). In addition to demonstrating that all elements were known in the prior art, the Office must also articulate a reason for combining the elements. *See, e.g., KSR* at 1741; *Omegaflex, Inc. v. Parker-Hannifin Corp.*, 243 Fed. Appx. 592, 595-596 (Fed. Cir. 2007). Further, the Supreme Court in *KSR* also stated that that "a court *must* ask whether the improvement is more than the predictable use of prior art elements according to their established functions." (emphasis added) *See KSR* at 1740. Therefore, in addition to showing that all

elements of a claim were known in the prior art and that one of ordinary skill in the art had reason to combine them, the Office must also provide evidence that the combination would have a reasonable expectation of success. That a combination of elements would be a "predictable success" is a critical factor in a determination of obviousness. This principle is illustrated in three Supreme Court cases (*United States* v. *Adams*, 383 U.S. 39, 40 1966; *Anderson's-Black Rock, Inc.* v. *Pavement Salvage Co.*, 396 U.S. 57, 60-62, 1969 and *Sakraida* v. *AG Pro, Inc.*, 425 U.S. 273, 282 1976) decided prior to KSR, and is a recurring theme of *KSR*. The Supreme Court in *KSR* stated that in order for a combination of elements to be patentable "the combination must do more than yield a *predictable* result" (emphasis added).

The new claims require determining the expression level of a target gene in a tissue sample obtained from a human subject, where the expression level of the target gene is determined by providing a polynucleotide complementary to an intronic sequence of a target gene. The Applicants submit that, in order for the claimed method to be a predictable success, one of ordinary skill in the art would have to have possessed knowledge that: a) intron sequences could be detected *and* b) that the level of intron sequence is correlative with the amount of mature mRNA of the target gene.

"A person of ordinary skill in the art is…presumed to be one who thinks along the lines of *conventional wisdom* in the art" (*Standard Oil Co. v. American Cyanamid Co.* 774 F.2d 448, 454 (Fed. Cir. 1985) (emphasis added). Further, MPEP § 2134.X.D.3 directs, "[t]he totality of the prior art must be considered, and proceeding contrary to *accepted wisdom* in the art is evidence of nonobviousness" (emphasis added).[1]

The Applicants submit that, at the time of filing, the claimed method would not have been a predictable success in view of the totality of the prior art because it was the prevailing wisdom that intronic RNA was rapidly degraded and therefore was not detectable and not

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[1] MPEP § 2134.X.D.3 "Proceeding Contrary to Accepted Wisdom Is Evidence of Nonobviousness. The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness" (citing *In re Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986)).

correlative with mRNA of the target gene. The totality of the prior art at the time of filing of the instant application indicates that spliced introns are rapidly degraded and that measurement of the expression level of an intronic sequence would not yield quantitative information about the expression of the target gene from which the intronic sequence originates.

For example:

- Thomas et al. (J. Virology 2002 76, 532-540) states: "This is in contrast to typical **cellular introns** that **are rapidly degraded following excision** from the pre-mRNA". See Exhibit A.

- Krummenacher et al. (J. Virology 2003 71, 5849-70) states: "Introns **are usually rapidly degraded** by a multistep process involving nucleases and specialized debranching enzymes". See Exhibit B.

- Mukerjee et al (Virology 324, 2004 340-9) states: "In contrast to other cellular **introns that are rapidly degraded following excision** from primary transcripts, the half-life of the 2-kb LAT intron has been measured to be 24 h in transiently transfected cells". See Exhibit C.

- Sharp (Cell 1994 77:805-815; Nobel Lecture) states: "This contrasts with the situation *in vivo* in which intron RNAs are almost always **rapidly degraded**". See Exhibit D.

- Nam et al (Mol. Cell. Biol. 1997 17 809-818) states: "The excised intron lariat RNA is **rapidly degraded in vivo**, with a half-life of only a few seconds". See Exhibit E.

- Hollander et al (Nuc. Acid Res. 1999 27 2345-2353) states: "**Efficient degradation of excised intron RNAs is important**, since free introns can cause toxicity by interactions with other cellular RNAs". See Exhibit F.

(Emphasis added in all quoted sections.) All references cited above are of record in this case. A page from each of the references showing the relevant passage is supplied herewith in the Exhibits section of this response.

In light of the totality of the prior art, it would not be clear to one of ordinary skill in the art that the isolated reports of a few detectable introns (e.g., *Clement*[2] and *Coleclough*[3], *both also* of record) were not simply peculiarities of the experimental methods by which the studies were carried out. The Applicants believe that the references discussed above adequately show that, at the time of filing, intron sequences were thought to be rapidly degraded and therefore would have been useless for quantitatively evaluating target gene expression.

In attempting to establish the rejection, the Examiner dismisses *Padgettt*[4] for being 15 years older than the other references discussed by the Applicants. The age of *Padgett* is noted. However, *Padgett* is only one among many references published in the years preceding the filing date, which taken as a whole clearly indicate what the Applicants believe to be the accepted wisdom at the time of filing, i.e. that introns are rapidly degraded. As such, *Padgett* should not be ignored simply because of its age.

Thomas[5] on the other hand, is used by the Examiner to support this rejection because it describes a spliced intron that can be detected. However, the intron detected by *Thomas* is an intron in the genome of *Herpes simplex* virus type 1 (HSV-1), i.e., the genome of a *virus*, not a cellular genome. The detection of this HSV-1 intron appears to be so unexpected that the authors

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[2] Clement, J.Q. et al. (2001) J. Biol. Chem. 276, 16919-16930. The Applicants also note that Clement states "Research in this area has been hindered by the widely held view that most vertebrate **introns are too unstable to be detectable**" and "A widely held believe is that spliced introns accumulate at low levels because they are **rapidly degraded (within seconds)** at their site of origin in the nucleus". See Exhibit G.

[3] Coleclough, C. and Wood, M. (1984) Mol. Cell. Bio. 4, 2017-2022. The Applicants also note that Coleclough states, with reference to IgGκ introns: "**These molecules are nonetheless ephemeral**, having half lives probably of only a few minutes". See Exhibit H.

[4] Padgett, R.A. (1986) Ann. Rev. Biochem. 55, 1119-50.

[5] Thomas, D.L. et al. (2002) J. Virology 76, 532-40.

postulate that this viral intron has evolved to be stable so that it can sequester cellular splicing factors, thereby shutting down general cellular splicing. (*See Thomas,* page 538, col. 2, middle paragraph). In view of *Thomas'* initial surprise and subsequent explanation, the Applicants believe that *Thomas* merely highlights the prevailing wisdom that excised introns are rapidly degraded because they are deleterious to the cell. Thus, rather than supporting the rejection, *Thomas* supports the Applicant's arguments.

Moreover, as noted above, merely detecting the presence of an intron would not lead one of skill in the art to practice the claimed method with a "prediction of success" because the claimed method requires not only that intron sequences can be detected, but also that the level of intron sequence is correlative with the amount of mature mRNA. Since *Thomas* does not suggest that the level of intron sequence is correlative with the amount of mature mRNA, one of skill in the art would not predict that the claimed method would be a success. Rather, since Thomas suggests that stable intron sequences are exceptional, and further implies that stability of the HSV intron is particular to the virus' strategy for shutting down host cell splicing, one of skill in the art would expect a lack of correlation between intron level and mature mRNA level. In fact, intron derived sequences are the only viral sequences readily detectable in host neurons latently infected with HSV and exon sequences that would be associated with mature mRNA are not detectable. Thus, taken as a whole, *Thomas* supports Applicant's arguments.

Moreover, *Duvick* does not teach that which *Fodor* lacks. This is evidenced by the fact that *Duvick* is cited by the Examiner solely to teach "detecting intron RNA and that the level of detected intron RNA would be proportional to...the transcription rate." (*See*, OA at p. 12.) *Duvick* teaches the use of U-tags inserted into the natural sequences of target genes as reporters in a method to conveniently assay expression of the target gene in cell lines. *Duvick* asserts, citing *Clement*, that U-tags would be useful as reporter sequences when introduced into intron sequences of the target gene. However, *Duvick* provides no evidence regarding the detectability of a U-tags inserted into introns of target genes and no evidence that the expression of such a U-tag correlates with the expression of exon sequences of the target gene. As noted by the Examiner, *Duvick* cites *Clement* in order to support the idea that introns persist in cells with reasonable half lives. However, there is nothing in *Clement* that indicates that the expression

level of any of the *Pem* introns studied is proportional to the expression level of a *Pem* exon, which would be a prerequisite for attempting the claimed method with a reasonable expectation of success.

It is worth noting that the art cited by the Examiner, such as *Clement* and *Duvick,* did not alter the accepted wisdom in the field. In 2004, *Ng* published a study of a 2-kilobase latency associated transcript (2-kb LAT) of the Herpes simplex virus type 1 (HSV-1). (Ng AK et al. (2004) J. Virol. 78, 12097–12106). In their introduction these authors summarize prior research, "**Surprisingly** (emphasis added) and perhaps of importance, the half-life of the 2-kb LAT is measured in hours, instead of seconds…The latter is the half-life unit associated with most introns, whose lariats are normally efficiently debranched and then degraded. (Sharp PA et al. (1987) Cold Spring Harbor Symp. Quant. Biol. 52:277-285)". The Nobel Prize winning work of Philip Sharp and colleagues was a key contribution to the accepted wisdom regarding intron-degradation in the late 1980s and early 1990s. In summary of their own results, Ng et al. (2004) suggest "…that the accumulation of the2-kb intron in tissue culture and in vivo is, at least in part, due to the nonconsensus branchpoint sequence in the LAT intron." (*See Ng*, p.12097, abstract) In a mutant virus, a three-nucleotide change in the branchpoint to a branchpoint consensus sequence reverses the unusual stability of the intron, suggesting that its stability is a functional specialization of this particular intron. Like Thomas, Ng's discussion highlights the prevailing wisdom at the time of his publication, that introns are rapidly degraded, and provides an explanation of why the viral intron under discussion is an exception to the accepted wisdom.

Similarly, in 2006, *Kulezsa and Shenk* published their research concerning the accumulation of a 7.2-kb viral intron in cytomegalovirus infected cells. (Kulesza, CA and Shenk T (2006) Proc. Nat. Acad. Sci. 103, 18302-18307). In discussing their research, the authors state, "The fact that the 7.2-kb RNA accumulates to easily detectable levels in infected cells suggests that it is **more stable than most introns**." (Emphasis added). Again, these authors provide an explanation of the unusual stability of the intron by carrying out additional investigations that "identified a hairpin sequence near the 3′ end of the 7.2-kb intron that contributes to its stable retention".

In view of the above, the cited references do not support the rejection of claim 104. Claims 105-114 depend, directly or indirectly, from claim 104, and thus inherit the aforementioned limitations. For these reasons, a rejection of the new claims is unsupported by the cited references.

Claims 25, 28-30, 32, 33, 36-39, 44, 55-58, 61-66, and 102

Claims 25, 28-30, 32, 33, 36-39, 44, 55-58, 61-66, and 102 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Dannenberg (US20010029018 A1) in view of Duvick (USPN 7,026,123). Claims 25, 28-30, 32, 33, 36-39, 44, 55-58, 61-66, and 102 have been canceled, therefore this rejection is moot and should be withdrawn. To the extent that this rejection applies to the new claims, Applicants respectfully traverse this rejection.

Dannenberg does not teach that which Duvick lacks, as is evidenced by the fact that Dannenberg is cited by the Examiner solely to teach a method for extracting total RNA from formalin-fixed, paraffin-embedded tumor biopsy tissue, followed by reverse transcription and real-time PCR to quantitate gene expression of specific genes. Dannenberg does not teach a method that comprises a step hybridizing the polynucleotide to intronic RNA or a nucleic acid produced therefrom to form a complex as is required by the method of claim 104.

The Applicants believe that this argument is addressed more fully by the discussion set forth above. Claims 105-114 depend, directly or indirectly, from claim 104, and thus inherit the aforementioned limitations. For these reasons, a rejection of the new claims is unsupported by the cited references..

Claim Rejections under 35 U.S.C. § 103- Dannenberg in view of Duvick and Dai

Claims 67, 68, 71, 74, and 103 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Dannenberg (US20010029018) in view of Duvick (USPN 7,026,123) and Dai (US20030223374. Claims 67, 68, 71, 74, and 103 have been canceled, therefore this rejection is moot and should be withdrawn. To the extent that this rejection applies to the new claims, Applicants respectfully traverse this rejection.

The Applicants believe that the failure of Dannenberg and Duvick to teach all the elements of claim 104 have been addressed by the discussion set forth above. Moreover, Dai

does not teach what Dannenberg and Duvick lack as is evidenced by the fact that the Examiner has relied on Dai solely to teach "measuring gene expression of CEGP1," "statistical analysis," and "determining whether the likelihood of long-term survival without the recurrence of breast cancer has increased or decreased." (*See*, OA at p. 23.) Claims 105-114 depend, directly or indirectly, from claim 104, and thus inherit the aforementioned limitations. For these reasons, a rejection of the new claims is unsupported by the cited references.

Claim Rejections under 35 U.S.C. § 103- Dannenberg in view of Duvick, Dai and Genbank

Claims 59 and 60 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Dannenberg (US20010029018) in view of Duvick (USPN 7,026,123), Dai (US20030223374), Genbank entry 8052236, and Buck et al. (1999). Claims 59 and 60 have been canceled, thus this rejection is moot and should be withdrawn. To the extent that this rejection applies to the new claims, Applicants respectfully traverse this rejection.

The Applicants believe that the failure of Dannenberg, Duvick, and Dai to teach all the claim limitations of claim 104 is addressed by the discussion set forth above. Moreover, Genbank entry 8052236 does not teach what Dannenberg, Duvick, and Dai lack, as is evidenced by the fact that the Examiner has relied on it solely to teach "a genomic sequence comprising CEGP1 gene, including introns." (*See*, OA at p. 25.) Similarly, Buck is cited by the Examiner solely to provide "evidence of the equivalence of primers." Claims 105-114 depend, directly or indirectly, from claim 104, and thus inherit the aforementioned limitations. For these reasons, a rejection of the new claims is unsupported by the cited references.

CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone James Keddie at (650) 833-7723.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number GHDX-007.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: December 3, 2008

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Enclosures: Exhibits A-H

IDS to cite references not yet cited

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